JACC Vol. 18, No. 4
October 1991:911–8

Demonstration of Myocardial Reperfusion Injury in Humans: Results of a Pilot Study Utilizing Acute Coronary Angioplasty With Perfluorochemical in Anterior Myocardial Infarction

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Reperfusion may limit the amount of potentially salvageable myocardium through the introduction of cellular elements into previously ischemic but viable myocardium (reperfusion injury). It has been demonstrated that intracoronary infusion of a 20% intravascular perfluorochemical emulsion (Fluosol) significantly reduces infarct size and results in improved left ventricular function in the canine model. This pilot study was performed to explore the existence of myocardial reperfusion injury in humans.

Utilizing Fluosol as a probe in conjunction with emergency coronary angioplasty, 26 patients presenting within 4 h with a first anterior myocardial infarction were randomized to emergency angioplasty or angioplasty followed by a 30-min intracoronary infusion of Fluosol at 40 ml/min. Global and regional ventricular function were assessed immediately and a mean of 12 days after successful angioplasty with contrast ventriculography. Infarct size was semiquantitated with thallium-201 single-photon emission computed tomography (SPECT) images before discharge. Twelve patients (six undergoing angioplasty alone, six treated with angioplasty and Fluosol) had an occluded infarct-related vessel (Thrombolysis in Myocardial Infarction [TIMI] grade 0 to 1) at the time of emergency catheterization and were included in the final analysis.

At 12 days after successful angioplasty, the improvement in regional ventricular function was greater in patients receiving adjunctive therapy with intracoronary Fluosol versus those undergoing angioplasty alone utilizing both the radial shortening and centerline method, respectively (23 ± 3.1% vs. 8 ± 2.3%, $p < 0.02$; and −1.6 ± 0.4 vs. −2.9 ± 0.2 SD/chord, $p < 0.05$). Tomographic infarct size expressed as a percent of the left ventricle was also reduced in Fluosol-treated patients (3.5 ± 2.2% vs. 18.3 ± 4.7%, $p < 0.05$). No significant differences in collateral blood flow, extent of coronary artery disease or residual stenosis after angioplasty were observed.

This preliminary study suggests that myocardial reperfusion injury may be an important factor in limiting myocardial salvage in patients undergoing reperfusion. These findings have important clinical implications because adjunctive therapy may further amplify the beneficial effects of mechanical or pharmacologic reperfusion. Additional prospective randomized trials must be done to confirm and extend these preliminary results.

(J Am Coll Cardiol 1991;18:911–8)

The use of numerous thrombolytic agents and percutaneous transluminal coronary angioplasty has established reperfusion therapy as routine treatment of acute myocardial infarction. Early reperfusion reduces the incidence of sudden cardiac death and lowers long-term cardiac mortality rates (1–4). The effects of reperfusion on infarct size and ventricular function have been less striking. Successful thrombolysis has resulted only in a modest improvement in global left ventricular function in some studies, predominantly in those patients treated within 3 to 6 h (5–9). Similarly, early reperfusion (<1.5 or <3.5 h) fails to prevent Q waves on the electrocardiogram (ECG) or persistent defects on thallium tomographic images, respectively (10,11).

Experimental studies (12,13) have demonstrated that restoration of blood flow to previously ischemic but reversibly injured cardiac cells may result in irreversible injury to these cells—so-called reperfusion injury. Perfluorochemicals are substances with a small particle size, low viscosity and high oxygen-carrying capacity. We previously demonstrated (14,15) that intracoronary administration of Fluosol, a 20% intravascular perfluorochemical emulsion (Alpha Therapeutic Corp.) 5 to 10 min after the onset of reperfusion in the closed chest canine model subjected to 90 min of proximal left anterior descending artery occlusion and either 24 h or

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Manuscript received January 31, 1991; revised manuscript received March 20, 1991, accepted April 5, 1991.

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0735-1097/91/$3.50

2 weeks of reperfusion significantly reduced infarct size and enhanced global and regional ventricular function. These studies, which temporarily linked an intervention in the perireperfusion period to myocardial salvage, established the occurrence of reperfusion injury in the experimental model.

The existence of reperfusion injury in humans is unproved. Studies utilizing captopril (16), the prostacyclin analogue Iloprost (17) and superoxide dismutase (18) failed to show beneficial effects on ventricular function in patients undergoing successful reperfusion. The specific aim of this pilot study was to determine the existence of myocardial reperfusion injury in patients presenting with acute myocardial infarction. The perfluorochemical Fluosol was utilized as a probe in conjunction with emergency coronary angioplasty to ascertain the effects of reperfusion injury on regional ventricular function and infarct size in patients with a first anterior myocardial infarction of <4 h duration in whom the status of vessel occlusion and exact timing of patency were known.

Methods

Patient selection. Twenty-six patients who presented with a first anterior myocardial infarction between July 1988 and June 1989 at three medical centers were enrolled. Patients were eligible for inclusion if they met the following criteria: age <75 years old, chest pain of >30 min duration unresponsive to sublingual nitroglycerin or nifedipine, or both, no previous myocardial infarction or coronary artery bypass surgery, electrocardiographic (ECG) evidence of ST segment elevation >0.1 mm in any four anterior leads (I, aVL, V_1 to V_6) and randomization in the emergency room within 4 h of the onset of chest pain. Predetermined exclusion criteria included: persistent hypotension (systolic blood pressure <90 mm Hg unresponsive to volume expansion), angiographic evidence of spontaneous reperfusion (Thrombolysis in Myocardial Infarction [TIMI] Trial grade >1) or significant (>50%) left main stenosis at the time of emergency catheterization, significant valvular disease and a history of hepatic or renal disease. The protocol and consent forms were approved by the Institutional Review Boards of the participating hospitals.

Protocol. After randomization, patients were taken for emergency cardiac catheterization. All patients received aspirin (325 mg orally) and lidocaine (1.5 mg/kg bolus injection followed by 2 to 4 mg/min intravenous infusion) before angiography. Subjects randomized to Fluosol received a test dose of 0.5 ml intravenously and were monitored for 10 min to assess changes in heart rate, blood pressure, respiratory rate and subjective responses. After insertion of arterial and venous sheaths, a bolus injection of heparin (10,000 U) was administered intravenously, followed by an infusion of 800 to 1,200 U/h titrated to maintain the partial thromboplastin time two or more times the control value. Left ventriculography was performed in the 30° right anterior oblique projection, followed by visualization of the right and left coronary arteries utilizing numerous standard and orthogonal views. If the left anterior descending artery was found to be occluded (TIMI grade 0 or 1 flow), acute angioplasty was performed utilizing a 0.014-in. (0.356 cm) guide wire and an over-the-wire balloon catheter. Typically, three to five inflations lasting 60 to 120 s were performed by using pressure sufficient to achieve full balloon expansion. Once adequate anterograde flow was established (TIMI grade 2 or 3), the system was withdrawn in the angioplasty group and repeat coronary angiography was performed in identical views before angioplasty. In patients randomized to Fluosol after angioplasty, the balloon was withdrawn proximal to the site of prior occlusion and an intracoronary infusion of Fluosol commenced utilizing a Medrad injector (Medrad Inc.) at a rate of 40 ml/min for 30 min (total volume 1,200 ml). The Fluosol emulsion was prepared and oxygenated to achieve a partial pressure of oxygen (Po_2) ≥500 mm Hg before infusion as previously described. Right heart pressures were measured intermittently with a Swan-Ganz catheter. Repeat angiography was also performed in the Fluosol group after removal of the angioplasty system.

All patients were then transferred to the cardiac intensive care unit and were maintained on therapeutic doses of lidocaine and heparin for 24 to 36 h. Aspirin (325 mg) and diltiazem (90 to 180 mg/day) were given orally during hospitalization. Beta-adrenergic blocking agents were withheld until after hospital discharge. Vascular sheaths were removed on the 2nd hospital day, after which the patients were progressively allowed to ambulate. Patients underwent 24-h Holter monitoring, thallium-201 single-photon emission computed tomography (SPECT) and repeat cardiac catheterization and ventriculography 7 to 14 days after successful angioplasty. All patients were followed up for a mean of at least 12 months to determine various clinical outcome variables.

Angiographic and ventriculographic data. All immediate and follow-up coronary angiograms and ventriculograms were reviewed by an experienced angiographer unaware of the treatment group. The severity of coronary stenosis was measured using a caliper method from the view that demonstrated the most severe lesion. Patients were categorized as having single-, double- or triple-vessel disease when an important lesion (defined as ≥75% reduction of intraluminal diameter) was present in one or more major epicardial coronary arteries. The perfusion status of the infarct-related vessel was graded utilizing the TIMI trial criteria (TIMI grade 0 to 3) (19). Collateral blood flow to the left anterior descending artery was graded on a scale of 0 to 3, depending on the degree of distal opacification of the occluded vessel (20).

Global and regional ventricular function were determined from end-diastolic and end-systolic left ventricular endocardial contours during a well opacified normal sinus beat before reperfusion and at 10 to 14 days after successful angioplasty by an observer who had no knowledge of patient data. Global ejection fraction was determined by the area-length method (21). Regional ventricular function was deter-

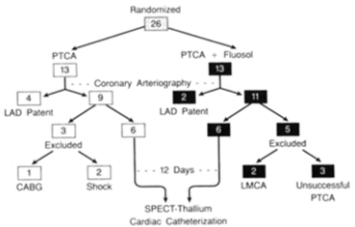


Figure 1. Flow chart of the study group. Fourteen of the 26 patients were excluded from final analysis as shown in the diagram. CABG = emergency coronary artery bypass surgery; LAD = left anterior descending artery; LMCA = left main coronary artery stenosis >50%; shock = development of cardiogenic shock within 24 h of reperfusion; PTCA = percutaneous transluminal coronary angioplasty; SPECT = single-photon emission computed tomography.

mined utilizing both a computerized centerline and radial shortening method. Wall motion for the infarct and noninfarct zones was initially determined by the chord method described by Sheehan et al. (22). Regional wall motion in the anterior wall was calculated as the mean motion of half of the most abnormally contracting contiguous chords and expressed in standard deviations (SD) per chord from a normal data bank. Modifications to this program were made to graphically display mean chordal shortening for each treatment group. Regional function was also analyzed with a radial shortening method with customized software previously validated in our laboratory (14). Thirty-six radii were constructed from the midpoint of the aortic valve plane and apex of the heart. The ischemic zone was defined as the largest number of contiguous radii that were akinetic or dyskinetic before angioplasty.

Thallium-201 tomography. Infarct size was estimated in eight patients from the perfusion defect measured by thallium-201 imaging (SPECT) 10 to 14 days after angioplasty as previously described (23). Patient images and quality control data were stored on floppy disks and transferred to a core laboratory for reconstruction and quantitative analysis.

Statistical analysis. All values are expressed as mean values ± SEM. Difference in global and regional ventricular function and perfusion defects between the two groups was determined with a Student's *t* test for paired data. Linear regression analysis was used to compare regional ventricular function and infarct size. Differences were considered significant at $p < 0.05$.

Results

Twenty-six patients met the entry criteria and were enrolled in the study (Fig. 1). Fourteen patients were excluded because of the presence of a patent left anterior descending artery at the time of catheterization (TIMI grade >1), unsuccessful angioplasty, left main stenosis or the development of fatal cardiogenic shock within 24 h of reperfusion. Twelve patients (six in each group) were included in the final analysis. The mean age was similar in both groups and the majority were men (Table 1). The time to successful reperfusion was similar in the two groups.

Table 1. Clinical and Angiographic Data in 12 Patients*

	PTCA (n = 6)	PTCA + Fluosol (n = 6)
Age (yr)	57.5 ± 11.7	55.3 ± 9.4
Gender (no.)	5 M, 1 F	5 M, 1 F
Time to reperfusion (h)	4.1 ± 0.5	3.3 ± 0.4
TIMI grade after PTCA	2.8 ± 0.2	2.8 ± 0.2
Diameter stenosis (%)		
Before PTCA	100	100
After PTCA	24 ± 2	18 ± 4
No. of vessels >50% stenosis	1.8 ± 0.4	1.8 ± 0.4
Collateral score	0.8 ± 0.5	1.1 ± 0.3
Thrombolytic agent (no. of patients)	2	1
Time to repeat catheterization (days)	10.5 ± 1	11.8 ± 1.9

*No differences were observed between groups. PTCA = percutaneous transluminal coronary angioplasty alone; PTCA + Fluosol = angioplasty followed by intracoronary infusion of Fluosol; TIMI = Thrombolysis in Myocardial Infarction.

Hemodynamic and angiographic data (Tables 1 and 2). Heart rate, systolic blood pressure and myocardial oxygen consumption as estimated from the rate-pressure product were similar in both groups. An increase in pulmonary capillary wedge pressure was observed at the end of the Fluosol intracoronary infusion. The left anterior descending artery was occluded proximally after the first diagonal branch in all patients at the time of emergency catheterization and this was associated with TIMI grade 0 or 1 flow as determined by the inclusion criteria. No statistically significant differences were noted in the extent of coronary artery disease, TIMI grade flow or residual diameter stenosis after emergency angioplasty. Time to reperfusion tended to be less and collateral grade greater in the Fluosol group, but did not reach significance. Two patients in the angioplasty group received intracoronary recombinant tissue-type plasminogen activator (rt-PA) and one in the Fluosol group received intracoronary streptokinase for angiographically visible intracoronary thrombus.

Ventriculographic data (Fig. 2 to 6). Suitable ventriculograms were obtained in all 12 patients before angioplasty and in 11 patients at the follow-up study. Global and regional ventricular function was obtained from radionuclide ventriculography in the other patient. Global ejection fraction was similar in both patient groups before angioplasty, with a trend to improvement in patients receiving Fluosol (54 ± 5% vs. 42 ± 4%, p = NS) (Fig. 2). Chordal shortening in the ischemic and nonischemic zones is shown in Figure 3. Chordal shortening was similar in the ischemic zone in both

Table 2. Hemodynamic Variables in the Two Treatment Groups

	Before Reperfusion		Reperfusion		Reperfusion 30 min		12 Days	
	P	P + F	P	P + F	P	P + F	P	P + F
Heart rate (beats/min)	80 ± 4	81 ± 5	86 ± 3	83 ± 5	81 ± 5	88 ± 6	80 ± 5	81 ± 5
Systolic blood pressure (mm Hg)	124 ± 5	132 ± 7	116 ± 18	108 ± 7†	113 ± 9	114 ± 5†	116 ± 9	129 ± 7
RPP ($\times 10^3$)	9.9 ± 0.8	10.6 ± 0.9	9.6 ± 1.3	9.0 ± 0.8	8.9 ± 0.8	10.3 ± 1	9.8 ± 1	10.6 ± 0.9
PA (mm Hg)*	22 ± 0	23 ± 4	NA	30 ± 3	NA	36 ± 2†	NA	NA
PCW (mm Hg)*	18 ± 1	19 ± 2	NA	25 ± 3	NA	31 ± 1†	NA	NA
LVEDP (mm Hg)	19 ± 5	25 ± 3	NA	NA	NA	NA	13 ± 4	18 ± 3

*Only measured in three patients undergoing coronary angioplasty (PTCA) alone; †$p < 0.05$ vs. before reperfusion. LVEDP = left ventricular end-diastolic pressure; NA = not obtained; P = angioplasty alone; P + F = angioplasty plus Fluosol; PA = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; RPP = rate-pressure product.

patient groups before reperfusion (−3.9 ± 0.3 vs. −3.5 ± 0.2 SD/chord, p = NS). A significant improvement in regional ventricular function occurred in the Fluosol group a mean of 12 days after angioplasty (−1.6 ± 0.4 vs. −2.9 ± 0.2 SD/chord, $p < 0.05$). No differences were noted in the nonischemic zone. Normalized wall motion for each group is shown graphically in Figure 4. Regional ventricular function in the ischemic zone remained <2 SD from a normal population base, whereas >50% of the chords in the ischemic zone in the Fluosol group fell within 2 SD of the mean. Regional ventricular function was also evaluated with a radial shortening method and is illustrated for the combined groups and individual patients in Figures 5 and 6. A significantly greater improvement in shortening occurred in the Fluosol group at the follow-up study (23 ± 3.1% vs. 8 ± 2.3%, $p < 0.02$).

Thallium scintigraphy (Fig. 7 and 8). Infarct size was estimated from the thallium perfusion defect in eight patients and expressed as a percent of the left ventricle. A smaller infarct size was noted in patients given intracoronary perfluorochemical compared with those undergoing angioplasty alone (3.5 ± 2.2% vs. 18.3 ± 4.7%, $p < 0.05$) (Fig. 7). The correlation between infarct size and radial shortening at 2 weeks is shown in Figure 8. A tight correlation was noted between these variables ($r = -0.92$, $p < 0.001$).

Clinical outcome. The patients were followed up for a mean of 21 months. Intracavitary thrombus formation was demonstrated by two-dimensional echocardiography in two patients (one in each group). Two patients in each group underwent coronary artery bypass surgery for severe three-vessel coronary artery disease. Clinical heart failure necessitating the administration of digoxin and diuretic drugs occurred in two patients in the angioplasty group. One death occurred during the follow-up period in a patient randomized to Fluosol who was diagnosed as having carcinoma of the lung during the initial hospitalization. Although an autopsy was not performed, death was presumed to be due to metastatic disease.

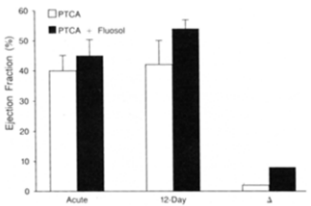


Figure 2. Global left ventricular ejection fraction measured by contrast ventriculography before angioplasty (PTCA) (acute) and a mean of 12 days after reperfusion. Ejection fraction tended to be higher in patients randomized to treatment with Fluosol. Δ = change.

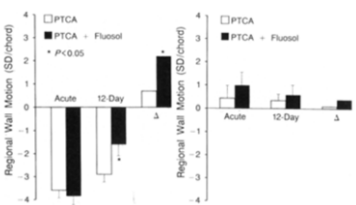


Figure 3. Regional wall motion in the central ischemic (**left panel**) and nonischemic regions (**right panel**) expressed as standard deviation (SD) per chord is illustrated. Note that before reperfusion, regional wall motion was similar in both groups in the central ischemic zone (derived from 50% of the chords lying in the infarct-related artery territory whose motion was most depressed compared with the normal patient group). Twelve days after angioplasty (PTCA), a significant improvement was observed in Fluosol-treated patients such that wall motion was within the normal population range. Relative hyperkinesia was noted in the nonischemic region in both groups acutely and at 12 days.

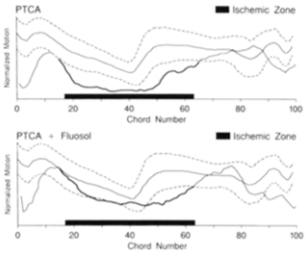


Figure 4. This graph illustrates normalized wall motion (**solid light line**) and 2 SD from the mean (**interrupted lines**) for a normal group utilizing the centerline method. Mean wall motion in the ischemic zone for the angioplasty (PTCA) group (**upper panel**) and angioplasty plus Fluosol group (**lower panel**) is shown by the **dark line** at 12 days after reperfusion. The ischemic zone was defined by the chords that fell below the normal range before angioplasty. In the angioplasty group (**upper panel**), wall motion remains <2 SD from the mean, whereas >50% of the chords in the Fluosol group (**lower panel**) fall within 2 SD of the mean.

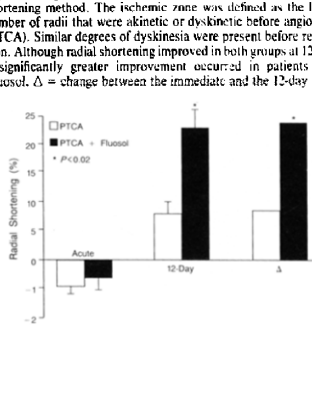
Discussion

Rationale for current study. Numerous studies (1–4) have demonstrated that successful coronary reperfusion reduces the in-hospital mortality rate and improves long-term survival in patients with acute myocardial infarction. However, the effects of reperfusion on infarct size and ventricular function have been less consistent. Improvements in global left ventricular function have been modest, with the greatest increase occurring in patients undergoing successful reperfusion within 3 h (5–9). Similarly, early reperfusion does not prevent the development of *Q* waves on the ECG (10). Furthermore, some studies (11) have failed to show a significant decrease in infarct size assessed by thallium-201 scintigraphy after successful reperfusion. Several agents administered after reperfusion enhance myocardial salvage in the experimental models (14,15,24,25). These studies (12,13) suggest that reperfusion itself may have potentially deleterious effects on the previously ischemic but potentially viable myocardium (reperfusion injury). Although the exact mechanism of reperfusion injury remains to be elucidated, current evidence (26–29) suggests that the introduction of oxygen and activated neutrophils results in accelerated microvascular injury through the release of oxygen-derived free radicals and various proteolytic enzymes.

Previous clinical studies. The existence of myocardial reperfusion injury in humans remains controversial. The observation that myocardial rupture was increased within the 1st 24 h in patients given intravenous streptokinase in the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI) study (30) suggests that reperfusion injury may be a real phenomenon. Studies utilizing intravenous captopril (16) and the prostacyclin analogue Iloprost (17) in conjunction with the tissue plasminogen activator did not significantly improve regional and global ventricular function 7 to 10 days after thrombolytic therapy. A randomized, double-blind trial (18) using human superoxide dismutase in patients undergoing emergency angioplasty within 6 h of acute infarction also failed to improve regional and global ventricular function within the 1st 4 to 6 weeks after reperfusion.

Current study. We (14,15) and others (31) previously demonstrated that intracoronary administration of the perfluorochemical Fluosol, a potent antineutrophilic agent, significantly decreases infarct size and improves ventricular function in the canine model of reperfusion. No detrimental effects on infarct healing in the canine and rabbit models have been demonstrated with this agent (15,32). The current pilot study was performed to determine the existence of reperfusion injury in humans. Prospective inclusion and exclusion criteria were selected with the hope that the potential beneficial effects of adjunctive therapy beyond successful reperfusion alone would be maximal. First, only patients with anterior myocardial infarction were studied because this group has a large and more predictable perfusion bed at risk. Second, because the time course of reperfusion injury remains unknown, only patients with an occluded left anterior descending artery (TIMI grade 0 or 1 flow) on arteriography were included. We documented the exact time of successful reperfusion and confirmed continual patency at the follow-up study. Third, all medications were carefully standardized and beta-adrenergic blocking agents were withheld during hospitalization because they would influence ventricular function. Finally, we excluded patients with a prior infarct because previous infarctions would

Figure 5. Regional wall motion was also assessed utilizing a radial shortening method. The ischemic zone was defined as the largest number of radii that were akinetic or dyskinetic before angioplasty (PTCA). Similar degrees of dyskinesia were present before reperfusion. Although radial shortening improved in both groups at 12 days, a significantly greater improvement occurred in patients given Fluosol. Δ = change between the immediate and the 12-day study.



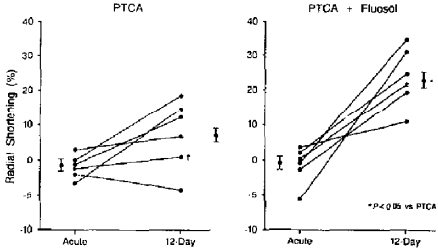


Figure 6. Radial shortening for individual patients treated with angioplasty (PTCA) or angioplasty plus Fluosol is shown. Although most patients demonstrated improved regional ventricular function at 12 days, adjunctive therapy with Fluosol resulted in a significantly greater improvement. †Wall motion assessed on radionuclide ventriculogram.

interfere with quantification of infarct size by perfusion scintigraphy.

Effect of Fluosol on reperfusion injury. Intracoronary infusion of the oxygenated perfluorochemical Fluosol during the early postangioplasty reperfusion period significantly improved regional ventricular function a mean of 12 days after reperfusion compared with that in patients undergoing emergency angioplasty alone. This improvement was associated with a decrease in infarct size in a subset of patients assessed with thallium-201 tomography. Variations in the site of coronary occlusion are unlikely to have caused the difference in perfusion defects because all patients had proximal occlusion of the left anterior descending artery after the first diagonal branch. Furthermore, a good correlation was noted between the degree of regional left ventricular dysfunction and infarct size by thallium-201 tomography. Randomization was effective in that both groups had comparable clinical and angiographic findings. These included the duration of ischemia, extent of left ventricular dysfunction before angioplasty, degree of angiographically visible collateral blood supply and residual stenosis in the culprit vessel after successful angioplasty. Selective infusion of Fluosol was well tolerated except for a transient increase in pulmonary capillary wedge pressure. Two patients in the control (angioplasty) group developed fatal cardiogenic shock within 24 h of successful reperfusion. During a mean follow-up period of 20 months, congestive cardiac failure occurred in two patients in the angioplasty group. One patient in the Fluosol group died of carcinoma of the lung, which was diagnosed soon after presentation.

Mechanism of action. Perfluorochemicals were initially developed as blood substitutes because of their small particle size, low viscosity and high oxygen-carrying capacity (33). The perfluorochemical Fluosol was recently approved by the Food and Drug Administration for alleviation of myocardial ischemia during balloon angioplasty (34). We previously demonstrated (35,36) that its administration in the canine model decreased neutrophil infiltration into the reperfused bed and this decrease was associated with relative

Figure 7. Infarct size expressed as a percent of the left ventricle was semiquantitated by SPECT-thallium scintigraphy in eight patients. Fluosol-treated patients manifested a reduction in infarct size a mean of 10 days after reperfusion. PTCA = percutaneous transluminal coronary angioplasty.

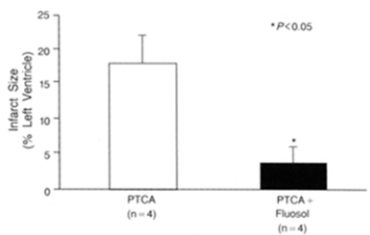
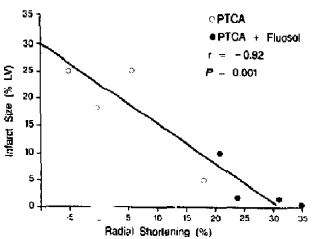


Figure 8. Relation between infarct size expressed as a percent of the left ventricle (LV) and radial shortening at 12 days is shown with linear regression analysis. A strong correlation was observed between these variables. PTCA = percutaneous transluminal coronary angioplasty.



structural and functional preservation of the microvasculature. Both intracoronary and intravenous administration of Fluosol resulted in a striking enhancement in myocardial salvage and improvement in ventricular function in the experimental model (14,15,31,36). Fluosol results in transient hypotension in the dog and this is associated with complement-mediated activation of circulating neutrophils. Because this reaction is rare in humans, we investigated the effect of Fluosol on human neutrophils in vitro and observed enhanced superoxide anion production within 1 min of exposure to the emulsion in the absence of complement (personal observations). These studies suggest that the beneficial effects of the agent in myocardial reperfusion injury may be secondary to removal of peripherally activated neutrophils from the coronary circulation during the initial period of reperfusion. Other potential beneficial effects include enhanced oxygen delivery to the microvasculature inaccessible to red blood cells because of the small particle size and low viscosity of Fluosol.

Study limitations. The objective of this study was to evaluate the occurrence of reperfusion injury in a carefully selected group of patients with a first anterior myocardial infarction in whom the exact time of successful reperfusion was known. A significant difference in several of the end points utilized was observed in the small number of patients studied. However, the study has several limitations. First, as a result of the small sample size, a large multicenter randomized study is needed to confirm these initial observations. Second, rapid intracoronary administration of a large volume of Fluosol results in transient volume overload and would not be a practical form of therapy in the majority of patients with evolving myocardial infarction. Because experimental studies (37) suggest that a slow infusion of the drug intravenously may be as efficacious as intracoronary administration, randomized studies utilizing Fluosol as an adjunctive agent with thrombolytic therapy appear warranted. Third, the occurrence of significant reperfusion injury in patients with inferior myocardial infarction needs further investigation because only patients with extensive anterior myocardial infarction were eligible for inclusion in the study. Finally, because myocardial stunning may persist for weeks after an ischemic event, longer-term assessment of regional ventricular function is needed (38).

Conclusions. This study is the first to demonstrate the occurrence of myocardial reperfusion injury in humans. Intracoronary administration of perfluorochemical (Fluosol) was utilized as a probe in patients with a large anterior myocardial infarction undergoing emergency angioplasty. Patients treated with Fluosol manifested improved regional ventricular function and a decrease in infarct size measured with thallium scintigraphy compared with results achieved with angioplasty alone. Therefore, myocardial reperfusion injury may be an important factor in limiting myocardial salvage in patients undergoing pharmacologic or mechanical reperfusion. This study has major clinical implications because it suggests that limitation of myocardial reperfusion injury is possible and may be a useful adjunctive therapy in patients with evolving myocardial infarction.

We thank Kathy Tuggle for expert secretarial assistance and John J. Murray, PhD for critical review of the manuscript.

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